

# Pd-Catalyzed Tandem $sp^2$ – $sp^3$ Coupling Reactions of Chiral Stannolanes: An Efficient Preparation of Optically Active Tetrahydrobenz[*f*]isoindoles

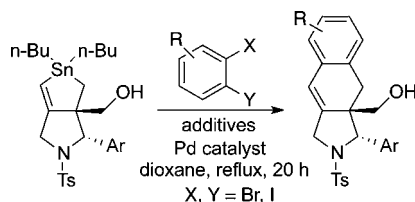
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## ABSTRACT



A novel double Migita–Kosugi–Stille coupling reaction with dihydrostannolanes, which are readily available from a radical cascade reaction, was achieved with dihalobenzenes in the presence of a palladium catalyst. Use of unsymmetrical 1-bromo-2-iodobenzene derivatives accomplished the double coupling reaction which gave tetrahydrobenz[*f*]isoindoles in a regioselective manner.

The Migita–Kosugi–Stille coupling reaction<sup>1</sup> is one of the most useful reactions in organic chemistry,<sup>2</sup> and it is frequently used in natural product synthesis and advanced

materials science.<sup>3</sup> The reaction employs organotin compounds as a coupling partner, with tributyltin-substituted aromatic or vinylic compounds being those most commonly used. Although the reaction provides an efficient coupling method, the coupling reactions are generally limited to the tin compounds that have an  $sp^2$ -carbon–tin ( $C_{sp^2}$ –Sn) bond. On the other hand, an  $sp^3$ -carbon–tin ( $C_{sp^3}$ –Sn) bond is rarely used as the coupling partner which was limited to methyl, allyl, and benzyl groups and  $\alpha$ -oxy- or  $\alpha$ -amino-substituted tin compounds.<sup>4</sup> For example, Falck utilized  $\alpha$ -acyloxytributylstannane in the coupling reaction.<sup>4a,c,d,f–h</sup> Chirality at the  $\alpha$ -carbon of an alkyl tin compound is maintained after the coupling. Vedejs and Jensen succeeded in introducing an amino-methyl group by the coupling reaction.<sup>4b,e</sup> Simple alkyl

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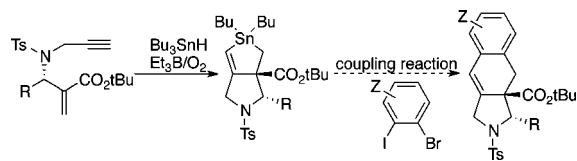
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groups without an activating group in the alkyltin compound are usually very inert in this chemical transformation except for methyl, allyl, and benzyl groups, although this type of transfer is often desired in organic synthesis.<sup>5</sup> Recently we developed a simple preparation of optically active dihydrostanolanes via radical cyclization<sup>6</sup> of chiral aza-Morita–Baylis–Hillman adducts.<sup>7</sup> The transformation passes through a radical S<sub>H</sub>2 process at the tin atom.<sup>8</sup> The obtained stannolanes contain C<sub>sp</sub>3–tin and C<sub>sp</sub>2–tin bonds in a single molecule and are potentially good candidates for the double coupling reaction under Pd-catalyzed conditions and could provide an efficient and novel synthesis of tetrahydrobenz[*f*]isoindoles (Scheme 1).<sup>9</sup>

**Scheme 1.** Double Migita–Kosugi–Stille Coupling Strategy for the Preparation of Tetrahydrobenz[*f*]Isoindoles

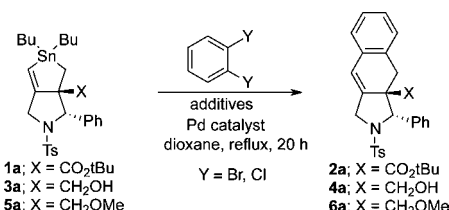


Tetrahydrobenz[*f*]isoindoles are of interest for their biological activities such as analgesic, antidepressant, anti-hypertensive, antiasthmatic, or antiallergic activities.<sup>10</sup> The preparation of this heterocyclic system has previously been achieved by intramolecular Diels–Alder reactions with styrene,<sup>11</sup> but the stereoselectivity was not really high. In this paper we report a novel double coupling reaction using a nonactivated C<sub>sp</sub>3–Sn bond to give optically active tetrahydrobenz[*f*]isoindoles. Two different aryl groups were also introduced using inter- and intramolecular double coupling conditions. A regioselective coupling reaction was also achieved using 1-bromo-2-iodobenzene derivatives.

We first examined the reaction of bicyclic dihydrostanolane ester **1a** (X = CO<sub>2</sub>*t*-Bu) with 1,2-dibromobenzene (Y = Br). The results are summarized in Table 1. We successfully obtained the desired double coupling product

**2a**, but the yield was only 18% (entry 1). Use of 100 mol % of Pd(*t*-Bu<sub>3</sub>P)<sub>2</sub> and 5 equiv of CsF improved the yield of **2a** to 41% (entry 2). The structure of **2a** was unambiguously determined by X-ray crystallographic analysis.<sup>12</sup> To improve the yield of the coupling products, we modified the ester group. Conversion of the ester to hydroxymethyl derivatives **3a** was achieved by simple DIBAL-H reduction of **1a**. Compound **3a** (X = CH<sub>2</sub>OH) was examined in the double coupling reaction with 1,2-dibromobenzene (Y = Br). The reaction performed under ambient temperature conditions did not progress, and starting materials were recovered.

**Table 1.** Optimization for Double Coupling Reaction of **1a**, **3a**, and **5a**



entry	Pd (mol %)	subst	Y	additives (equiv)	prod	yield (%) <sup>a</sup>
1	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> (10)	<b>1a</b>	Br	CsF (5)	<b>2a</b>	18
2	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> (100)	<b>1a</b>	Br	CsF (5)	<b>2a</b>	41
3	Pd(OAc) <sub>2</sub> (10) <sup>c</sup>	<b>3a</b>	Br	DABCO (3)	<b>4a</b>	48
4	Pd(OAc) <sub>2</sub> (10) <sup>d</sup>	<b>3a</b>	Br	DABCO (3)	<b>4a</b>	24
5	Pd(OAc) <sub>2</sub> (10) <sup>e</sup>	<b>3a</b>	Br	DABCO (3)	<b>4a</b>	26
6	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> (10)	<b>3a</b>	Br	—	<b>4a</b>	0 <sup>b</sup>
7	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> (10)	<b>3a</b>	Br	K <sub>2</sub> CO <sub>3</sub> (3)	<b>4a</b>	37
8	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> (10)	<b>3a</b>	Br	iPr <sub>2</sub> NEt (3)	<b>4a</b>	55
9	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> (10)	<b>3a</b>	Br	DABCO (3)	<b>4a</b>	76
10	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> (5)	<b>3a</b>	Br	DABCO (3)	<b>4a</b>	66
11	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> (2)	<b>3a</b>	Br	DABCO (3)	<b>4a</b>	66
12	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> (10)	<b>3a</b>	Cl	DABCO (3)	<b>4a</b>	0
13	Pd( <i>t</i> -Bu <sub>3</sub> P) <sub>2</sub> (10)	<b>5a</b>	Br	DABCO (3)	<b>6a</b>	48

<sup>a</sup> Isolated yield. <sup>b</sup> Complex mixture. <sup>c</sup> Xphos (32 mol %) was added. <sup>d</sup> PPh<sub>3</sub> (29 mol %) was added. <sup>e</sup> BINAP (16 mol %) was added.

The desired double coupling adduct **4a** was isolated in 48% yield when the reaction was carried out in the presence of Pd(OAc)<sub>2</sub> with Xphos and DABCO (entry 3).

(12) Crystallographic data for the structures **2** and **7a** have been deposited as CCDC 845992 and CCDC 915372, respectively.

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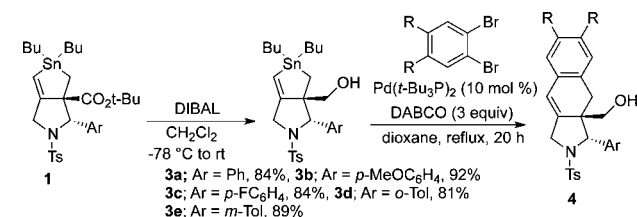
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Use of other ligands such as  $\text{PPh}_3$  and BINAP also progressed the reaction, but the yield of **4a** remained at a low level (entries 4 and 5). The absence of base in the reaction mixture gave a complex mixture (entry 6). DABCO afforded the best results for the reaction catalyzed by  $\text{Pd}(t\text{-Bu}_3\text{P})_2$  (entries 7–9). A catalyst loading could be reduced to 2 mol % with a slight loss of yield (entries 9–11). Use of dichlorobenzene failed to form double coupling adducts although the starting material was completely consumed (entry 12). Thus, we concluded that use of 10 mol %  $\text{Pd}(t\text{-Bu}_3\text{P})_2$  and 3 equiv of DABCO provided the optimal conditions for the double coupling reaction. Methyl ether **5a** also afforded the corresponding double coupling products **6a**, but the yield remained at a moderate level (entry 13). The existence of an OH group in **3a** probably activated the alkyl group transfer to progress the double coupling reaction.<sup>13</sup>

The aforementioned reaction conditions were applied to various compounds of general structure **3**, which were prepared by the reduction of **1** with DIBAL-H. The results are summarized in Table 2.

**Table 2.** Double Coupling Reaction for **3**



entry	substrate	Ar	R	4; yield (%) <sup>a</sup>
1	<b>3a</b>	Ph	MeO	<b>4b</b> ; 73
2	<b>3a</b>	Ph	F	<b>4c</b> ; 78
3	<b>3a</b>	Ph	Me	<b>4d</b> ; 64
4	<b>3b</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	H	<b>4e</b> ; 71
5	<b>3b</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	MeO	<b>4f</b> ; 64
6	<b>3b</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	F	<b>4g</b> ; 70
7	<b>3b</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	<b>4h</b> ; 75
8	<b>3c</b>	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	H	<b>4i</b> ; 73
9	<b>3c</b>	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	MeO	<b>4j</b> ; 56
10	<b>3c</b>	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	F	<b>4k</b> ; 67
11	<b>3c</b>	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	Me	<b>4l</b> ; 76
12	<b>3d</b>	<i>o</i> -Tol	H	<b>4m</b> ; 73
13	<b>3d</b>	<i>o</i> -Tol	MeO	<b>4n</b> ; 59
14	<b>3d</b>	<i>o</i> -Tol	F	<b>4o</b> ; 70
15	<b>3d</b>	<i>o</i> -Tol	Me	<b>4p</b> ; 70
16	<b>3e</b>	<i>m</i> -Tol	H	<b>4q</b> ; 66
17	<b>3e</b>	<i>m</i> -Tol	MeO	<b>4r</b> ; 65
18	<b>3e</b>	<i>m</i> -Tol	F	<b>4s</b> ; 73
19	<b>3e</b>	<i>m</i> -Tol	Me	<b>4t</b> ; 74

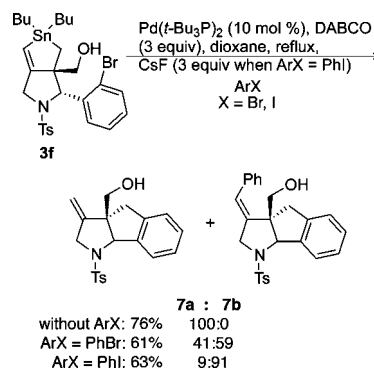
<sup>a</sup> Isolated yields.

The double coupling reaction with 1,2-bromoarenes took place smoothly, and the desired double coupling

products **4** were isolated in good yields. For example, treatment of **3a** with 1,2-dibromo-4,5-dimethoxybenzene smoothly produced **4b** in 73% yield as a single diastereomer. During the coupling reaction no scrambling of stereochemistry was observed and enantiomeric excesses of the starting materials were maintained in the products.

To explore the possibility of introducing two different aryl groups via the double coupling reaction, we examined compound **3f**, which we hoped would serve as a good candidate for a tandem coupling reaction (Scheme 2). Treatment of **3f** under similar conditions, in the absence of halobenzene (ArX), gave **7a** in 76% yield. The structure of **7a** was determined by X-ray crystallographic analysis.<sup>12</sup> To our surprise, an exo-methylene unit was introduced and an intramolecular coupling reaction occurred only at the  $\text{sp}^3$ -carbon site. We assume that the hydrogen source in **7a** might come from the OH in **3f** or water in wet dioxane. Compound **3f** underwent partial double coupling when treated with bromobenzene; the double coupling product **7b** was formed along with **7a** in a 61% total yield. The ratio of **7a**:**7b** was 41:59. To improve the selectivity of the reaction in favor of **7b** we examined iodobenzene instead. The reaction, in the presence of iodobenzene, under the same conditions, predominantly gave **7b** in 63% yield. The ratio between **7a** and **7b** now reached 9:91. Thus we achieved the introduction of two different aryl groups using inter- and intramolecular coupling reactions.

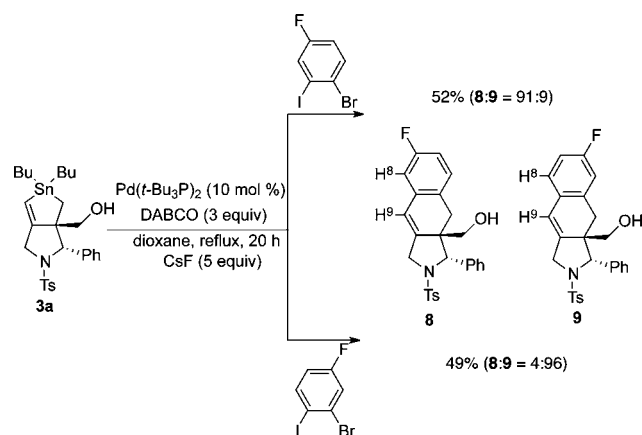
**Scheme 2.** Introduction of Two Different Aryl Groups Using Inter- and Intramolecular Coupling Reactions



We next examined the regioselective double coupling reaction with 1-bromo-2-iodobenzene derivatives (Scheme 3). For example, 1-bromo-4-fluoro-2-iodobenzene underwent regioselective coupling under the standard conditions using CsF, and coupling product **8** was isolated in 52% yield. The regioisomeric ratio of **8**:**9** was 91:9. Although TLC analyses indicated that other products were formed in the reaction, we could not isolate them because of their high polarity. On the other hand, 2-bromo-4-fluoro-1-iodobenzene gave its regioisomer **9** in 49% yield; compounds **8** and **9** were formed in 4:96 ratio. Both coupling reactions progressed in a highly regioselective manner. The structure of these compounds was unambiguously determined by NOE observation. Thus, H8 was unambiguously assigned from the

(13) An intramolecular activation in 2-(2-hydroxyprop-2-yl)phenyl-substituted alkylsilanes is reported; see: Nakao, Y.; Takeda, M.; Matsumoto, T.; Hiyama, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 444.

**Scheme 3.** Regioselective Double Coupling Reaction Using 1,2-Bromiodobenzenes



coupling constant between H8 and F. For example, H8 in compound **8** appeared at 6.66 ppm with a large  $J^{19\text{F}-1\text{H}}$  coupling constant of 9.2 Hz, while H8 in compound **9** was observed at 6.90 ppm with a moderate level of  $J^{19\text{F}-1\text{H}}$  coupling of 5.7 Hz. Signal enhancements for H9 were observed at 8% for **8** and 13% for **9** when H8 in **8** and **9** were irradiated, respectively. These results clearly suggested

(14) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132; see also ref 9.

that the double coupling reaction happened in a sequential manner. Thus, the iodine-attached carbon was selectively substituted by the  $\text{C}_{\text{sp}^2}$ -tin bond and the bromine-attached carbon was selectively substituted by the  $\text{C}_{\text{sp}^3}$  carbon. Addition of CsF was necessary to progress the reaction smoothly for iodobenzene derivatives.<sup>14</sup> Hence the double coupling reaction was readily controlled by the use of substituted 1-bromo-2-iodobenzene derivatives.

In conclusion we have successfully developed a new  $\text{C}_{\text{sp}^3}$ -Sn unit for the coupling partner of an intramolecular Migita-Kosugi-Stille coupling reaction and effectively prepared tetrahydrobenz[f]isoindoles in one step from an optically active stannolane, which was readily produced by a radical cascade reaction. Use of 1-bromo-2-iodobenzene achieved regioselective coupling reactions. The present methodology will provide a useful synthetic method and good information to progress nonactivated  $\text{C}_{\text{sp}^3}$ -Sn compounds for the palladium-catalyzed coupling partner.

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**Supporting Information Available.** Experimental procedures, compound characterization data, and CIF files. This material is available free of charge via Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.